



## Drug Delivery

ISSN: 1071-7544 (Print) 1521-0464 (Online) Journal homepage: <http://www.tandfonline.com/loi/idrd20>

# Montelukast medicines of today and tomorrow: from molecular pharmaceuticals to technological formulations

Jessica Silva Barbosa, Filipe A. Almeida Paz & Susana Santos Braga

To cite this article: Jessica Silva Barbosa, Filipe A. Almeida Paz & Susana Santos Braga (2016) Montelukast medicines of today and tomorrow: from molecular pharmaceuticals to technological formulations, Drug Delivery, 23:9, 3257-3265, DOI: [10.3109/10717544.2016.1170247](https://doi.org/10.3109/10717544.2016.1170247)

To link to this article: <http://dx.doi.org/10.3109/10717544.2016.1170247>



Accepted author version posted online: 24 Mar 2016.  
Published online: 11 Apr 2016.



Submit your article to this journal [↗](#)



Article views: 476



View related articles [↗](#)



View Crossmark data [↗](#)



Citing articles: 1 View citing articles [↗](#)

Full Terms & Conditions of access and use can be found at  
<http://www.tandfonline.com/action/journalInformation?journalCode=idrd20>



## REVIEW ARTICLE

# Montelukast medicines of today and tomorrow: from molecular pharmaceuticals to technological formulations

Jessica Silva Barbosa<sup>1,2</sup>, Filipe A. Almeida Paz<sup>2</sup>, and Susana Santos Braga<sup>1</sup><sup>1</sup>Department of Chemistry, QOPNA Research Unit, University of Aveiro, Aveiro, Portugal and <sup>2</sup>Department of Chemistry, CICECO Aveiro Institute of Materials, University of Aveiro, Aveiro, Portugal**Abstract**

Montelukast sodium is a leukotriene antagonist of growing interest as an alternative therapy for asthma across different age groups due to its bronchoprotective, anti-inflammatory and anti-allergic properties. Currently, montelukast is commercialized only in oral solid dosage forms, which are the favorite of adult patients but may pose challenges in administration to children of young age or patients suffering from dysphagia. This review presents a comprehensive revision of scientific reports and patents on emerging strategies for the delivery of montelukast. A common ground to these reports is the pursue of an enhanced montelukast performance, by increasing its bioavailability and physico-chemical stability. A wide variety of strategies can be found, from the formation of supramolecular adducts with cyclodextrins to encapsulation in nanoparticles and liposomes. The new dosage forms for montelukast are designed for non-enteric absorption, some for absorption in the oral cavity and another two being for local action in the nasal mucosa or in the pulmonary epithelium. The review describes the emerging delivery strategies to circumvent the current limitations to the use of montelukast that are expected to ultimately lead to the development of more patient-compliant dosage forms.

**Keywords**

Chronotherapeutic systems, cyclodextrins, drug stability, nano-encapsulation, oral delivery

**History**

Received 2 February 2016

Accepted 20 March 2016

**Introduction**

The discovery in 1979 of the implication of leukotrienes in the etiology of respiratory diseases and the elucidation of their structure triggered the search for novel compounds able to block leukotrienes as new treatments for asthma. For over a decade, the company Merck Frosst developed two research programs on the topic, one to find an inhibitor of the key biosynthesizing enzyme, 5-lipoxygenase, and the other to find a selective blocker of the Leukotriene D<sub>4</sub> receptor. These projects yielded six compounds, which were brought into human clinical trials and ultimately led to the release of montelukast (Figure 1) under the tradename Singulair. Today, montelukast treats millions of patients around the world with market sales estimated around 5 billion US dollars per year (Young, 2011).

Asthma, a chronic inflammation manifesting as shortness of breath, wheeze and chest tightness (Pawankar, 2014; Global Initiative for Asthma (GINA), 2015) is raising concerns in public health due to the increase in the incidence of cases over the last decades. The respiratory airways present hyperresponsiveness (AHR) to external stimulus and bronchoconstriction due to subepithelial fibrosis and smooth muscle hypertrophy and hyperplasia, which reduce the ventilation capacity of these airways (Lemanske & Busse, 2003; Adcock

et al., 2008; Kudo et al., 2013; Global Initiative for Asthma (GINA), 2015).

These pathophysiological alterations are triggered by inflammation mediators, such as cysteinyl leukotrienes (CysLTs) C<sub>4</sub> (LTC<sub>4</sub>), LTD<sub>4</sub> and LTE<sub>4</sub> that activate the cysteinyl-leukotriene 1 receptors (CysLT<sub>1</sub>Rs) existing in bronchial smooth muscle (Hamid et al., 2003; Wenzel, 2003). By blocking CysLT<sub>1</sub>R (Figure 2), montelukast is able to restore normal functionality and consequently improve lung function (Wenzel, 2003; Adcock et al., 2008). Montelukast has also anti-allergic action, thus protecting against allergen-induced asthma and preventing exercise-induced asthma (Leff et al., 1998; Phipatanakul et al., 2002).

**Marketed montelukast formulations**

Montelukast is generally well tolerated by patients and it is suitable for incorporation into oral dosage forms (Knorr et al., 1998; Pizzichini et al., 1999; Storms et al., 2001; Chorao et al., 2014). Noteworthy, this approach was a major improvement in drug administration when compared to the classic medicines for asthma treatment such as corticosteroids and bronchodilating agents, available only as inhalables.

In its original neutral form, montelukast is poorly soluble in water (0.2–0.5 µg/mL, 25 °C), with overall solubility increasing to 100–1000 µg/mL through the formation of a sodium salt, which is the commercialized form of this API.

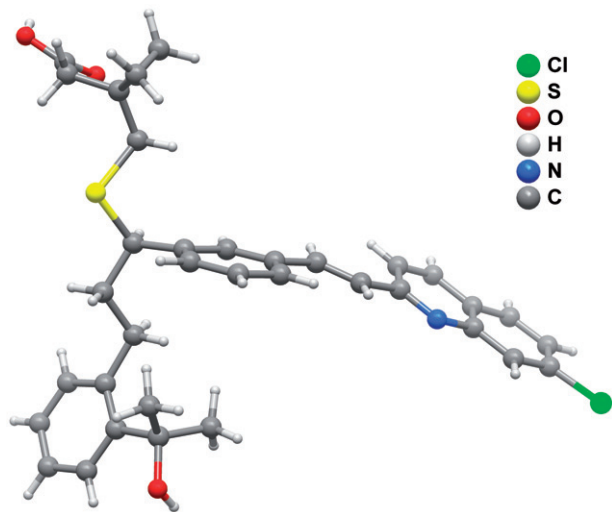


Figure 1. Molecular representation of montelukast (acid form). Redrawn from the atomic coordinates of the crystal structure of montelukast (Thun et al., 2009), available at the Cambridge crystallographic database (©CCDC 2002–2016).

Currently available dosage forms

Presently, montelukast sodium is available from a variety of pharmaceutical companies, either under the tradename Singulair® (by Merk) or as a generic API. The formulations are to be taken orally and comprise only solid dosage forms, namely tablets, chewable tablets and oral granules (Table 1).

Uses and limitations

The most important limitations to the use and formulation of montelukast are associated with its physico-chemical properties. Montelukast, both in the neutral and the salt form, is sensitive to light, temperature, humidity and oxidation (Al Omari et al., 2007; Okumu et al., 2008; Rashmitha et al., 2010). In this context, the presently available dosage forms are designed to minimize exposure to light and humidity, which explains why liquid formulations are not marketed to date.

Administration of montelukast to small babies is a challenge. The available formulation is the granules with compatibility guaranteed only for mixtures with the mother’s milk or milk formulas, after which they should be quickly administered. Furthermore, the oral granules have to be packed in individual, light- and air-proof sachets and, after opening, they should be ingested within 15 minutes. In the case of the chewable tablets, some formulations (including Singulair) contain aspartame as sweetener. Being thus a

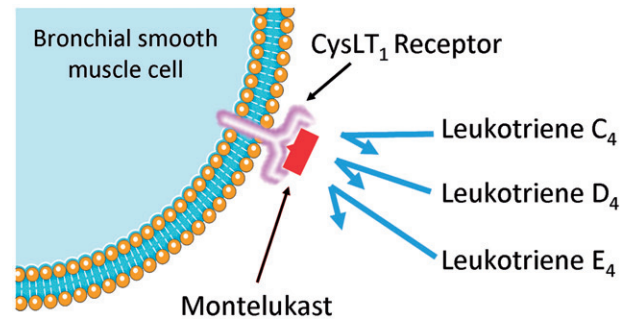


Figure 2. Interaction of montelukast with CysLT1R blocks the access to the active site for CysLTs, which are no longer able to trigger inflammation.

phenylalanine source aspartame-containing tablets are not recommended for patients with phenylketonuria (Merck & Co, 2015).

Pharmacokinetics from oral administration

Oral administration of montelukast implies that not all the dose contained in the tablet or granules reaches the blood-stream, due to losses during gastroenteric absorption and the effect of hepatic first pass metabolism, known to be the major cause of its relatively low bioavailability (61–73%, depending on the dose and on the concomitant food intake) (Cheng et al., 1996).

Montelukast undergoes extensive oxidative metabolism in the liver by the cytochrome P450 enzyme system, with a very significant contribution of the mono-oxidase CYP2C8 (72%), followed by CYP3A4 (16%) and CYP2C9 (12%), and it is excreted into the bile (Cheng et al., 1996; Filppula et al., 2011). Its permanence in the bloodstream is relatively short. Its plasmic concentration peaks at around 2 to 4 h after intake and it has a rapid elimination. The mean plasma half-life is of 2.7 to 5.5 h (Kearns et al., 2008).

Adverse reactions & drug interactions

Montelukast is generally well tolerated, although adverse reactions were reported, with stronger incidence in infants: headache, diarrhea, abdominal pain, nausea, fever and cough (Knorr et al., 1998; Lipworth, 1999; Simons et al., 2001; Storms et al., 2001; van Adelsberg et al., 2005). In adults, cases of hypersensitivity have been reported, leading to autoimmune vasculitis, hepatic eosinophilic infiltration and even anaphylaxis (Calapai et al., 2014).

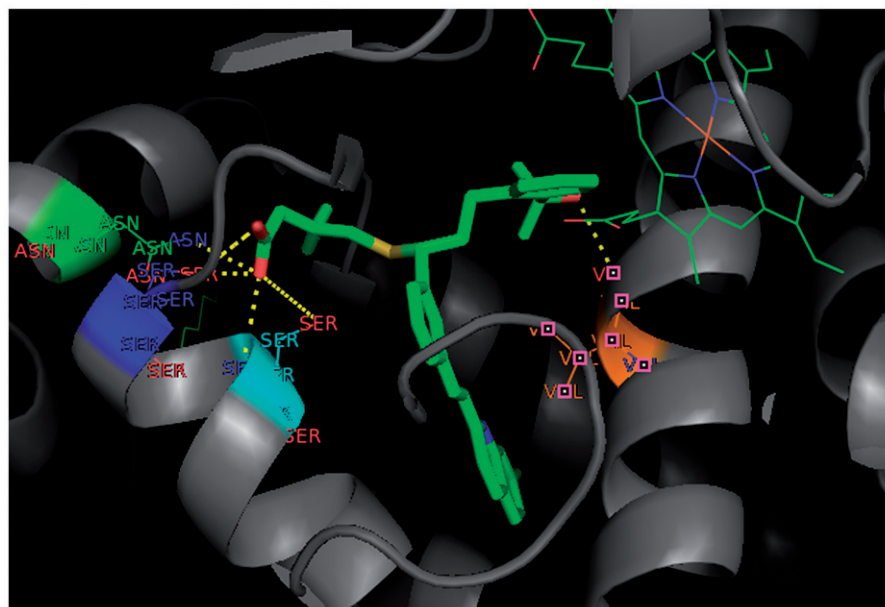
Reported drug interactions with montelukast refer to the reduction, by up to 40%, of its plasmic concentration when it

Table 1. Marketed formulations of montelukast, their doses, benefits and target age groups.

Dosage	Formulation	Benefits	Age group
4 mg	oral granules	Easy to swallow, dispersible and compatible with lactant’s milk <sup>a,b</sup>	6 months to 5 years
	chewable tablets		2–5 years
5 mg	chewable tablets	Suitable for youngsters <sup>b,c</sup>	6–14 years
10 mg	film coated tablets	Resistant to daylight <sup>b,c</sup>	≥15 years

<sup>a</sup>Migoya et al. (2004).  
<sup>b</sup>Storms (2007).  
<sup>c</sup>Al Omari et al. (2007).

Figure 3. Interaction of montelukast with CYP2C8. Drawn with the software PyMol (DeLano Scientific, Palo Alto, CA) from the atomic coordinates of montelukast CYP2C8 cocrystals (Agarwal et al., 2010), available at the protein data bank.



is being taken in tandem with phenobarbital, phenitoin or rifampin (Buck, 2015).

A report on interaction of montelukast with corticosteroids is also known. A patient taking montelukast and prednisone orally as a treatment for asthma, has gained 13 Kg in weight as the result of a severe peripheral edema, which was resolved upon discontinuation of the corticosteroid while maintaining treatment with montelukast. It is, thus, plausible to infer that montelukast has potentiated the retention of fluids caused by the corticosteroid (Geller, 2000).

The plasma concentration of montelukast may be exceedingly increased upon interaction with drugs that block the main enzyme responsible for its metabolism, CYP2C8. A known inhibitor of CYP2C8 is gemfibrozil (lipid regulating API), which, when co-administered with montelukast, increases its plasma concentration and may lead to rare cases of liver toxicity (Agarwal et al., 2010). Montelukast itself also has good affinity to CYP2C8 (although less than gemfibrozil) and the ability to inhibit CYP2C8. There is, thus, the possibility of interaction of montelukast with other APIs which are metabolized by this enzyme: troglitazone, rosiglitazone and pioglitazone (APIs for the management of diabetes), amodiaquine (anti-inflammatory and antimalarial), amiodarone (antiarrhythmic) and cerivastatin (cholesterol-regulating API).

The binding of montelukast to the enzyme CYP2C8 has already been demonstrated *in vitro* (Schoch et al., 2008), as depicted in the Figure 3. The chloroquinoline moiety is docked into a hydrophobic pocket, while the carboxylate group forms hydrogen bonds with serine and asparagine aminoacid residues of the enzyme and the third branch, composed of a tertiary alcohol bound to a phenyl, is positioned close to the heme iron.

### New formulations for montelukast

The very limited options available for the delivery of montelukast, along with the higher accessibility to this API

which followed the expiry of the patent for Singulair® in 2012 (Merck & Co, 2013) have triggered an increase in the studies aiming at the development of new formulations for this anti-asthmatic medicine. Nowadays we can find a variety of alternative and innovative formulations, which can be classified into three main categories, according to the involved technology:

(I) macroscale formulation uses macromolecules to disperse montelukast, increasing its solubility and embodying it with improved physico-chemical properties and bioavailability;

(II) nano-formulation relies on the incorporation of montelukast into nanoparticles to achieve higher stability and an improved pharmacokinetic profile;

(III) formulations at the molecular level use specific carriers, namely cyclodextrins, which are able to incorporate a molecule of montelukast, or a fragment of its molecule.

### Macromolecule-based formulations for improved oral delivery

These new forms of oral delivery are designed to quickly disintegrate, or even dissolve, in the mouth, emerging as attractive alternatives to the conventional formulations. They are particularly useful in pediatric, geriatric and bedridden patients who have difficulty in swallowing (Siddiqui et al., 2011). Furthermore, by making montelukast available for pre-gastric absorption, in the mouth, pharynx, and esophagus, these formulations help circumvent hepatic first-pass metabolism rendering higher the bioavailability.

#### Orally disintegrating tablets

Orodispersible tablets (ODTs) are designed to disintegrate in the mouth before swallowing. Initially defined as “a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”, there is still no consensus on the



maximum disintegrating time. USP's guidelines recommend a maximum of 30 seconds (Center for Drug Evaluation and Research (CDER), 1998), while many other sources cite 1 min as the limit for disintegration. The preparation of ODTs relies mainly on the use of an adequate dispersing agent. These excipients are strongly hydrophilic and receive the common name of 'superdisintegrant' (Figure 4) since they are able to ensure disintegration occurs within a very short period of time.

Successful montelukast formulations as ODTs were reported using as the dispersing agent a cellulose derivative, crosscarmellose sodium (Ac-Di-Sol®) (Chhajed et al., 2012; Sri et al., 2012), modified starch (sodium starch glycolate), the synthetic polymer croscopovidone (crosslinked N-vinyl-2-pyrrolidone) or a combination of these (Mahesh et al., 2012; Gupta et al., 2014; Shravani & Rao, 2014; Bhusnure et al., 2015). Some of the reported ODTs were found to require specialized packing and storage conditions (Mahesh et al., 2012), while another set of proposed formulations demonstrated to be stable at  $40 \pm 2^\circ\text{C}$  and a relative humidity of  $75 \pm 5\%$  for 3 to 6 months (Shravani & Rao, 2014). ODTs comprising an association of montelukast with taste-masked levocetirizine were also reported, with these having a very fast disintegration time of *c.a.* 16 seconds. Stability studies consisted in storing the montelukast/levocetirizine-containing ODTs in aluminum capped clear glass vials for three months at  $40 \pm 2^\circ\text{C}$  and a relative humidity of  $75 \pm 5\%$  and then measuring monthly their drug content and drug release profile. No significant differences were found ultimately

showing that the ODTs are stable over the three months period (Gupta et al., 2014).

#### Fast-dissolving oral films and buccal patches

A trendy alternative to the fast-dissolving tablets are oral thin films which have a more pleasant texture and a good shelf-life. Oral films can be designed to i) dissolve under one minute, being named fast-dissolving oral thin films, or ii) exhibit sustained release mucoadhesive buccal patches. Both formulations favor sublingual absorption, helping to bypass the hepatic first-pass metabolism and increasing bioavailability. Nonetheless, they are sensitive to environmental moisture and require a specialized package which rendered them less affordable and has limited their widespread use (Siddiqui et al., 2011).

Fast-dissolving films of montelukast, dissolving within 30 seconds and having a neutral surface pH, were reported by Ghorwade et al. In their package, these new formulations were demonstrated to be stable at  $40 \pm 2^\circ\text{C}$  and at a relative humidity of  $75 \pm 5\%$  for 3 months (Ghorwade et al., 2011). Another montelukast fast-dissolving film, developed by Khatoun et al., had a surface pH within 6.35–6.75 (Khatoun et al., 2014). Note that the salivary pH varies from 6.8 to 7.2, which implies that formulations with compatible pH are less prone to cause irritation of the oral mucosa.

Mucoadhesive buccal patches of montelukast allow a sustained release, with 60% to 90% of the API being released within the first 8 hours, as observed by *in vitro* studies (Rao & Suryakar, 2010; Rao et al., 2010; Rao & Suryakar, 2011; Mohamed et al., 2014). A study involving guinea pigs previously sensitized with histamine has demonstrated that the release of montelukast from mucoadhesive patches provides a protective effect against bronchoconstriction for a period of 6 h, whereas when it was administered as solution the protective effect lasted only one and a half hours (Soni et al., 2012a). Further optimization of the mucoadhesive patch was achieved by preparing a bilayer system. Each bilayer patch was loaded with only 5 mg of montelukast (half of the conventional daily dose for adults) since the second layer is designed to protect from leakage in the period of mucoadhesion and permits a unidirectional delivery through the buccal mucosa. *In vitro* tests have shown a quasi-linear and complete release of montelukast over eight hours (Soni et al., 2012b), but *in vivo* tests are required to prove that bioavailability from these bilayer patches is equivalent to that achieved with conventional tablets.

#### Encapsulation into nanoparticles

##### Polymeric nanoparticles for pulmonary delivery

The pulmonary route for drug delivery allows a reduction of the amount of drug administered to the patients, a decrease of the side effects and avoidance of the hepatic first pass metabolism. A handful studies have focused on the development of aerosol forms for the delivery of montelukast, using nanoparticles of chitosan or poly-lactic acid (PLA).

Chitosan [poly (1,4- $\alpha$ -D-glucopyranosamine)] is a biodegraded polysaccharide prepared by N-deacetylation of chitin

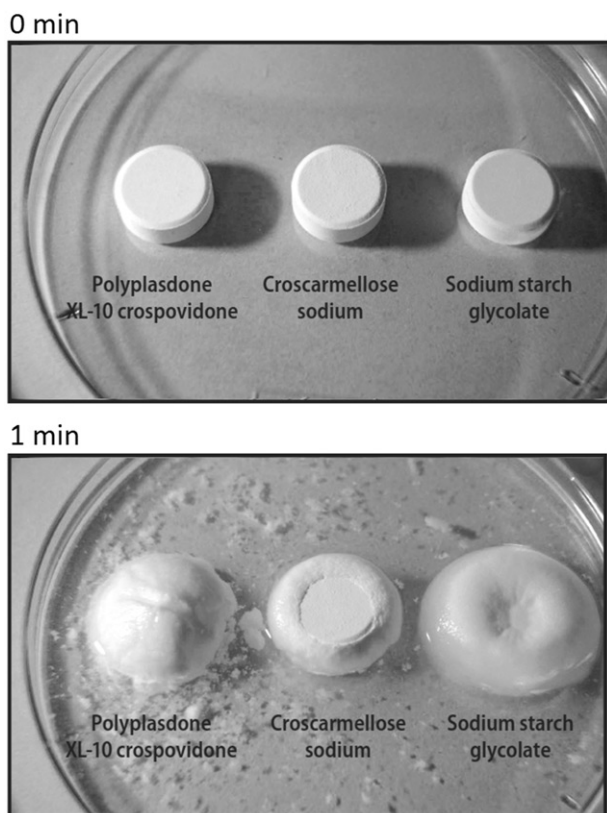


Figure 4. Disintegration, by contact with water, of placebo tablets made with the superdisintegrants croscopovidone (left), croscarmellose (center) and starch glycolate (right). Adapted from "Polyplasdone™ croscopovidone superdisintegrants product overview" leaflet, by Ashland Inc.

which has been used in the construction of nanosized drug carriers and gene transfer vectors. Chitosan nanoparticles have been the focus of considerable attention due to their many advantages, including good stability and simple preparation (Agnihotri et al., 2004; Nagpal et al., 2010). In addition, chitosan nanoparticles can facilitate the transposition across cellular barriers and transiently cause opening of the tight junctions between epithelial cells (Hu et al., 2011). The formulation of chitosan nanoparticles for the pulmonary delivery of montelukast allowed its protection from degradation and a sustained release for 24 hours (Inamdar et al., 2013).

A word of caution is, however, required on the use of chitosan nanoparticles. The aforementioned ability to facilitate permeation of epithelia means there is the possibility that chitosan nanoparticles will translocate from the gastrointestinal tract, nasal cavity, or alveolar sacs into the systemic circulation (Hu et al., 2011). Toxicity evaluation with 200 nm chitosan nanoparticles on zebrafish embryos has demonstrated signs of physiological and oxidative stress, translating into decreased hatching rates, embryo malformations and dose-dependent increase in mortality rate (Hu et al., 2011).

Poly lactic acid (PLA) is a bio-derived, biocompatible and biodegradable polymer, approved as GRAS by the FDA in the 1970s (Code of Federal Regulations, 2016). It is an excellent material for biomedical applications including sutures, clips, and drug delivery systems (Xiao et al., 2012). Patel et al. produced montelukast-loaded large porous PLA particles and demonstrated that these particles are capable of reducing the inflammation of asthmatic mice, the morphological changes associated with it and the airway hyperreactivity, thus resulting in a more efficient therapy for asthma than the conventional oral dosage forms (Patel et al., 2014).

#### *Lipid nanoparticles with a solid matrix*

Lipid nanoparticles are made from physiological lipids, which are both biocompatible and biodegradable, thus having huge advantages over the polymeric nanoparticles that may cause toxic effects as the polymer is degraded *in vivo* (Das & Chaudhury, 2011). Lipids improve bioavailability since they are able to promote oral absorption *via* selective lymphatic uptake. Lipid nanoparticles with a solid matrix have demonstrated to possess a high drug loading (both hydrophilic and lipophilic drugs) and hassle-free large-scale production (Das & Chaudhury, 2011; Patil-Gadhe & Pokharkar, 2014). The small size of the particles, ideally between 120 and 200 nm, helps avoid blood clearance by the reticuloendothelial system (*i.e.*, liver and spleen filtrations are avoided) (Das & Chaudhury, 2011). They are divided into two categories, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs).

SLNs were developed in the 1990s, being the first generation of lipid-based nanoparticles. They are not really solid, but they can contain drug crystals, super-cooled mixed phases and crystallised lipids which tend to change to lower energy forms over time (Figure 5). Long-term storage is, thus, difficult because of the risk of instability. Not rarely, the particles burst open and release their load (zur Muhlen et al., 1998; Mehnert & Mader, 2001). Encapsulation of

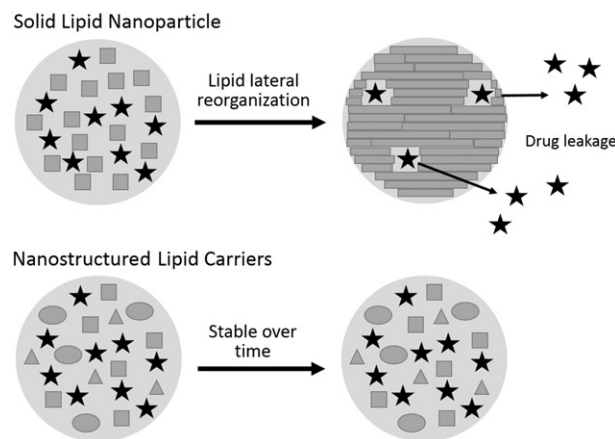


Figure 5. Schematic representation of SLNs and NLCs.

montelukast into SLNs allowed to achieve entrapment efficiencies between 48 and 85%, a variation which depends strongly on the employed lipid. The size range of the SLNs with montelukast lied within the 50–80 nm, and it was demonstrated that these particles were stable in storage for up to 30 days (Priyanka & Sathali, 2012).

NLCs are the second generation of lipid-based nanoparticles. They were developed aiming at addressing the instability and release issues associated with SLNs. NLCs are hybrid nanoparticles blending lipids with very different structures in order to have a matrix ‘as imperfect as possible’ (which is more stable) (Das & Chaudhury, 2011). Usually, solid lipids and oils are mixed to produce NLCs that are still solid at ambient temperature as well as at body temperature (Müller et al., 2002). NLCs allow a higher loading capacity, with a lower API leakage and they are suitable for incorporation in final dosage forms such as tablets or capsules (Das & Chaudhury, 2011; Patil-Gadhe & Pokharkar, 2014; Weber et al., 2014). Encapsulation of montelukast into NLCs allowed obtaining an entrapment efficiency of 96.1%, corresponding to a montelukast concentration of 2.02 mg/mL. Administration of the montelukast-loaded NLCs to Wistar rats has demonstrated a bioavailability increase of 143 fold (compared to a montelukast aqueous solution), and a sustained release profile over 24 h (Patil-Gadhe & Pokharkar, 2014). The montelukast-loaded NLCs were also tested for pulmonary delivery: controlled and sustained montelukast release was demonstrated *in vitro* by tests on simulated lung fluid (Patil-Gadhe et al., 2014).

#### **Molecular encapsulation with cyclodextrins**

Cyclodextrins (CDs), discovered by Villiers when studying the bacterial degradation of starch (Villiers, 1891), are small rings of 1,4-linked  $\alpha$ -D-glucose, typically occurring in Nature with six to eight units, being coined  $\alpha$ -CD,  $\beta$ -CD and  $\gamma$ -CD. Chemical modification of these native cyclodextrins affords a variety of derivatives with different physico-chemical and biological properties. Of the existing derivatives, now more than 1500 (Nitalikar et al., 2012), the most relevant to pharmaceutical and biomedical applications is 2-hydroxypropyl- $\beta$ -cyclodextrin (HP $\beta$ CD), which combines excellent aqueous solubility and solubilizing properties with a good

tolerability *in vivo*, being an FDA-approved excipient for powders, oral liquid and injectable formulations (Food and Drug Administration, nd). Methylated derivatives are also excellent solubilizers and include permethylated  $\beta$ -CD (TRIMEB) and randomly methylated  $\beta$ -cyclodextrins (RAMEB and CRYSMEB, having different number of methyl groups per cyclodextrin unit). TRIMEB, due to its hemolytic action is not suitable for internal use, being used in topical formulations for its ability to enhance drug permeation into cells and across the skin and mucosa. RAMEB is still pending approval for pharmaceutical uses. Other cyclodextrin derivatives that may be used in pharmaceutical applications include 2-hydroxypropyl- $\gamma$ -cyclodextrin (HP $\gamma$ CD) and sulfo-butylether- $\beta$ -cyclodextrin (SBE $\beta$ CD), although their high cost still renders them less attractive as excipients.

#### *Cyclodextrins as functional excipients in solid formulations*

Cyclodextrins, both native and derivatives, are patented ingredients for the preparation of porous microparticles for the delivery of several APIs, including montelukast. The increased area-to-surface ratio and lower density of these microparticles is claimed to afford higher flowability, suspension rate and bioavailability (Healy et al., 2007).

Cyclodextrins can also be used to help formulate solid particles. In a Chinese patent, HP $\beta$ CD is used as an excipient in the preparation of solid particles with a combination of two APIs, montelukast and calcium citrate. The product is claimed to have a 'better effect' and to avoid 'damage to vessel wall of the patient' (Chen et al., 2012).

#### *Liquid formulations*

Liquid formulations are the preferred administration form for pediatric medicines, particularly in the case of lactants. Liquid formulations for montelukast are, however, currently unavailable in the market, a feature easily understood because of the aforementioned hydrolytical instability, further potentiated by exposure to light. The well-known protective action of CDs against these two damaging agents makes them the perfect approach to circumvent the issue. A handful of studies and patents on the utility of CDs in the preparation of liquid formulations of montelukast are already available. One of these contains native CDs, along with other solubilizers and stabilizers, and claims to have 'superior stability, taste and flavor' (Kwon et al., 2015).

The inclusion of montelukast into chemically modified CDs in aqueous solution was first demonstrated in 2006, using heptakis-(2,6-di-O-methyl)- $\beta$ -cyclodextrin (DIMEB) as the host (Duran Meras et al., 2007). Nevertheless, only in 2015 a stable aqueous oral solution of montelukast was achieved, using HP $\beta$ CD to include the API. The report shows that HP $\beta$ CD brings a slight increase in the solubility of montelukast sodium and, more importantly, a significant improvement of its stability, with less than 1% degradation and no precipitation occurring after 2 months. Moreover, the oral solution showed similar plasma concentrations and pharmacokinetic parameters to the commercial granules, thus suggesting that it is bioequivalent to them. Concerning storage, it remains physically and chemically stable at 25 °C for at least 12 months (Kim et al., 2015).

HP $\beta$ CD and/or  $\gamma$ -CD are also claimed to help solubilize and protect montelukast from oxidation in a formula associating it with the antihistamine loratadine. Aiming at nasal delivery, the invention consists of a liquid to semi-solid formulation (gel, suspension or emulsion) (Bhattacharya et al., 2003).

### **Chronotherapeutic approaches**

Resulting from a combination of chronobiology and pharmaceuticals, chronopharmaceutics is devoted to the design and evaluation of drug delivery systems that release an API at a rhythm that ideally matches the biological requirement of a given disease therapy. The chronotherapeutic approaches take into account the circadian fluctuations associated with chronic diseases, namely diabetes, arthritis, ulcers and asthma. In asthmatic patients, the airway resistance increases progressively during the night and the lung function reaches a low point in the early morning. A drug delivery system capable of being administered at night but releasing the drug only in the first hours of the morning is thus a much more effective therapy (Padmaxi et al., 2012; Ranjan et al., 2014). Chronotherapies for asthma are already available with the corticosteroids prednisolone/cortisone (Dutimelan<sup>®</sup>) (Durrington et al., 2014), theophylline (Uniphyll<sup>®</sup>) (Leslie, 1986) and the  $\beta$ 2 agonists albuterol (Proventil Repetabs<sup>®</sup>, Volmax<sup>®</sup>), terbutaline (Bambuterol<sup>®</sup>) and tulobuterol (Hokunalin Tape<sup>®</sup>) (Durrington et al., 2014). For montelukast, chronotherapeutic systems under study are currently based on the pulsatile drug release systems. The release occurs in a 'pulse', meaning that the API is released suddenly after a well-defined lag time or time gap, according to circadian rhythm of disease states (Bhutkar et al., 2013). No drug is released from the device within this lag time.

A reservoir system with erodible barrier coating was developed for montelukast, providing a lag time of 5 hours before release. The system consists of press-coated tablets with a coating layer of hydrophilic polymers that swell and erode over the five hours to expose an inner core tablet. These core tablets, containing the superdisintegrant Ac-Di-Sol<sup>®</sup>, release *in vitro* 70% of the montelukast within 5 mins, followed by the maximum release in 15 mins (Padmaxi et al., 2012). Another proposed system, also based on press-coated tablets, had a shorter lag time, of four hours (Janugade et al., 2009). Besides the tablets, there is also a report on pulsatile release capsules for montelukast, allowing the release of montelukast sodium after 4 hours of administration (Ranjan et al., 2014). These formulations may be helpful for preventing the worsening of asthma occurring in the early morning, from 4 a.m. up to 8 a.m. (Hetzel & Clark, 1980), with proposed administration time around 12 p.m. of the previous day.

### **Conclusion**

This review illustrates how the work performed by various research groups spread throughout the world constitutes a solid foundation to engineer, in the near future, innovative formulations and delivery systems for montelukast, which may bring significant improvements to two main weaknesses: the bioavailability and the instability of this API.



A number of these drug delivery approaches are devoted to the improvement of the bioavailability, based mainly on oral delivery in order to increase pre-gastric absorption and thus avoid loss of drug due to the hepatic-first pass metabolism. This metabolic action is responsible for the reductions of 30–40% of the plasmic concentration of montelukast. The proposed new delivery strategies include orodispersible tablets and fast-dissolving thin films for quick release and onset of action. Nevertheless, the most promising dosage form for absorption in the oral cavity is, in our opinion, the bucoadhesive patches, which were shown to provide a prolonged action, avoiding bronchoconstriction for a period of up to 6 h.

Nanoencapsulation techniques bring a two-in-one solution for montelukast delivery, as they protect it from degradation and simultaneously offer dramatic increases in bioavailability providing that the nanoparticles have the right size to elude liver uptake, that is, between 120 and 200 nm. Montelukast-loaded NLCs proved to be excellent delivery systems in Wistar rats, bringing a 143-fold increase in bioavailability.

Systems designed for local action of montelukast constitute a growing trend in delivery, with PLA nanoparticles being proposed as carriers in the case of pulmonary delivery and cyclodextrins as molecular capsules for the preparation of topic nasal formulations.

A special highlight should be given to the use of cyclodextrins. Literature data is consensual concerning their benefic function towards the aqueous solubility of montelukast, either in the acid or in the salt form, which, in most of the cases, will be enough to lower the amount of drug needed to achieve therapeutically-significant bioavailabilities. Finally, and most importantly, the demonstrated ability of HP $\beta$ CD to improve the stability of montelukast in aqueous solution to the exposure of light will certainly unlock the door to the development of liquid forms for montelukast, which is of the utmost relevance in pediatry.

## Declaration of interest

The authors acknowledge Fundação para a Ciência e a Tecnologia (FCT, Portugal), European Union, QREN, European Fund for Regional Development (FEDER), through the program COMPETE, for general funding to the QOPNA research unit (FCT UID/QUI/00062/2013) and CICECO-Aveiro Institute of Materials, POCI-01-0145-FEDER-007679 (FCT Ref. UID/CTM/50011/2013), financed by national funds through the FCT/MEC and when appropriate co-financed by FEDER under the PT2020 Partnership Agreement.

## References

Adcock IM, Caramori G, Chung KF. (2008). New targets for drug development in asthma. *Lancet* 372:1073–87.

Agarwal VK, Mchutchison JG, Hoofnagle JH, et al. (2010). Important elements for the diagnosis of drug induced liver injury. *Clin Gastroenterol Hepatol* 8:463–70.

Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. (2004). Recent advances on chitosan based micro and nanoparticles in drug delivery. *J Control Release* 100:5–28.

Al Omari MM, Zoubi RM, Hasan EI, et al. (2007). Effect of light and heat on the stability of montelukast in solution and in its solid state. *J Pharm Biomed Anal* 45:465–71.

Bhattacharya S, Chhabada S, Lagu K. Intranasal pharmaceutical compositions comprising an antihistamine and a leukotriene inhibitor. World Patent WO 2003101434 A2, 2003 Dec 11.

Bhushure OG, Nandgave AV, Gholve SB, et al. (2015). Formulation and evaluation of fast dissolving tablet of montelukast sodium by using QbD approach. *Indo Am J Pharm Res* 5:1092–104.

Bhutkar AM, Khochage SR, Raut I, et al. (2013). A review on pulsatile drug delivery system. *Am J Pharm Tech Res* 3:18–35.

Buck ML. (2015). Montelukast: A review of recent studies in pediatric asthma and allergic rhinitis. *Pediatr Pharmacother* 21. Available at: <https://med.virginia.edu/pediatrics/wp-content/uploads/sites/237/2015/12/201507.pdf> [last accessed 7 Jan 2016].

Calapai G, Casciaro M, Miroddi M, et al. (2014). Montelukast induced adverse drug reactions: a review of case reports in the literature. *Pharmacology* 94:60–70.

Chen L, He Y, Jiang Y, et al. Inventors. Beijing Hanmi Pharmaceutical Co., LTD, Assignee. Montelukast sodium combined medicine particle for treating cancer, allergic rhinitis and allergic asthma comprises two active components of montelukast sodium and citric acid calcium. Chinese Patent CN102688238 A. 2012 June 18.

Cheng H, Leff JA, Amin R, et al. (1996). Pharmacokinetics, bioavailability, and safety of montelukast sodium (MK 0476) in healthy males and females. *Pharm Res* 13:445–8.

Chhajer M, Tiwari D, Malve A, et al. (2012). Formulation development and evaluation of montelukast sodium orodispersible tablets: a new trend in asthma treatment. *Int J Pharm Res Sci* 1:127–39.

Chorao P, Pereira AM, Fonseca JA. (2014). Inhaler devices in asthma and COPD an assessment of inhaler technique and patient preferences. *Respir Med* 108:968–75.

Das S, Chaudhury A. (2011). Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. *AAPS Pharm Sci Tech* 12:62–76.

Duran Meras I, Espinosa Mansilla A, Rodriguez DA. (2007). Complexation study of cinalukast and montelukast with cyclodextrins. *J Pharm Biomed Anal* 43:1025–32.

Durrington HJ, Farrow SN, Ray DW. (2014). Recent advances in chronotherapy for the management of asthma. *Chronophysiol Therap* 4:125–35.

FDA database of inactive ingredients for approved drug products. Available at: <http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm> [last accessed 27 Aug 2014].

Filppula AM, Laitila J, Neuvonen PJ, Backman JT. (2011). Reevaluation of the microsomal metabolism of montelukast: major contribution by CYP2C8 at clinically relevant concentrations. *Drug Metab Dispos* 39:904–11.

Geller M. (2000). Marked peripheral edema associated with montelukast and prednisone. *Ann Intern Med* 132:924.

Ghorwade V, Patil A, Patil S, et al. (2011). Development and evaluation of fast dissolving film of montelukast sodium. *World J Med Pharm Biol Sci* 1:6–12.

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. Available at: <http://www.ginasthma.org/>.

Gupta MM, Gupta N, Chauhan BS, Pandey S. (2014). Fast disintegrating combination tablet of taste masked levocetizine dihydrochloride and montelukast sodium: formulation design, development, and characterization. *J Pharmaceutics* 2014:568320.

Hamid Q, Tulic MK, Liu MC, Moqbel R. (2003). Inflammatory cells in asthma: Mechanisms and implications for therapy. *J Allergy Clin Immunol* 111:S5–S12.

Healy AM, McDonald B, Corrigan OI, Tajber L. Inventors. Trinity College Dublin, Healy AM, McDonald B, et al., Assignees. Porous microparticles of organic compound preparation by combining organic compound(s) with volatile solvent system, and drying the system thus formed to provide pure porous microparticles of organic compound. World Patent WO 2007086039 A1, 2007 Aug 2.

Hetzel MR, Clark TJ. (1980). Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax* 35:732–8.

Hu YL, Qi W, Han F, et al. (2011). Toxicity evaluation of biodegradable chitosan nanoparticles using a zebrafish embryo model. *Int J Nanomed* 6:3351–9.

Inamdar BP, Kathawala KJ, Parikh AY, et al. (2013). Formulation, development and characterization of Chitosan nanoparticles of



- montelukast sodium for site specific drug delivery in management of asthma. *Int J Drug Formul Res* 4:87 101.
- Janugade BU, Patil SS, Patil SV, Lade PD. (2009). Formulation and evaluation of press coated montelukast sodium tablets for pulsatile drug delivery system. *Int J ChemTech Res* 1:690 1.
- Kearns GL, Lu SS, Maganti L, et al. (2008). Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol* 48:502 11.
- Khatoun N, Rao NR, Reddy BM. (2014). Formulation and evaluation of oral fast dissolving films of montelukast sodium. *Int J Pharm Sci Res* 5:1780.
- Kim YH, Kim DW, Kwon MS, et al. (2015). Novel montelukast sodium loaded clear oral solution prepared with hydroxypropyl beta cyclodextrin as a solubilizer and stabilizer: enhanced stability and bioequivalence to commercial granules in rats. *J Incl Phenom Macrocycl Chem* 82:479 87.
- Knorr B, Matz J, Bernstein JA, et al. (1998). Montelukast for chronic asthma in 6 to 14 year old children: A randomized, double blind trial. Pediatric montelukast study group. *JAMA* 279:1181 6.
- Kudo M, Ishigatsubo Y, Aoki I. (2013). Pathology of asthma. *Front Microbiol* 4:16.
- Kwon TK, Choi YK, Yan XW, et al. Inventors. Hanmi Pharmaceutical Co., Ltd, Assignee. Liquid formulation comprising montelukast or pharmaceutically acceptable salt thereof and method for preparing same. World Patent WO 2015093847 A1, 2015 June 25.
- Leff JA, Busse WW, Pearlman D, et al. (1998). Montelukast, a leukotriene receptor antagonist, for the treatment of mild asthma and exercise induced bronchoconstriction. *N Engl J Med* 339:147 52.
- Lemanske Jr. RF, Busse WW. (2003). 6. Asthma. *J Allergy Clin Immunol* 111:S502 19.
- Leslie S. (1986). The Contin delivery system: dosing considerations. *J Allergy Clin Immunol* 78:768 73.
- Lipworth BJ. (1999). Leukotriene receptor antagonists. *Lancet* 353: 57 62.
- Mahesh E, Kumar GBK, Ahmed MG, Kumar KP. (2012). Formulation and evaluation of montelukast sodium fast dissolving tablets. *Asian J Biomed Pharm Sci* 2:75 82.
- Mehner W, Mader K. (2001). Solid lipid nanoparticles production, characterization and applications. *Adv Drug Deliv Rev* 47:125 32.
- Merck & Co., Inc. (2015). Prescribing information for Singulair®. ©Merck 1998 2012. Available at: <http://www.merck.com/index.html>. [last accessed 19 Jan 2016].
- Merck & Co., Inc. (2013). Annual report pursuant to section 13 or 15(d) of the securities exchange act of 1934. Available at: <http://www.merck.com/investors/financials/form 10 k 2012.pdf>. [last accessed 20 Oct 2015].
- Migoya E, Kearns GL, Hartford A, et al. (2004). Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. *J Clin Pharmacol* 44:487 94.
- Mohamed IM, El Moneim EA, Afify MR, Mekhael MKG. (2014). Formulation and evaluation of anti asthmatic drug montelukast in mucoadhesive buccal patches. *J Coastal Life Med* 2:907 14.
- Müller RH, Radtke M, Wissing SA. (2002). Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv Drug Deliv Rev* 54:S131 55.
- Nagpal K, Singh SK, Mishra DN. (2010). Chitosan nanoparticles: a promising system in novel drug delivery. *Chem Pharm Bull (Tokyo)* 58:1423 30.
- Nitalikar MM, Sakarkar DM, Jain PV. (2012). The cyclodextrins: a review. *J Curr Pharm Res* 10:1 6.
- Okumu A, DiMaso M, Lobenberg R. (2008). Dynamic dissolution testing to establish in vitro/in vivo correlations for montelukast sodium, a poorly soluble drug. *Pharm Res* 25:2778 85.
- Padmaxi B, Karwa P, Patel K, et al. (2012). Formulation and evaluation of time controlled drug delivery system of Montelukast sodium. *Int J Pharm Innovations* 2:1 12.
- Patel B, Gupta N, Ahsan F. (2014). Aerosolized montelukast polymeric particles an alternative to oral montelukast alleviate symptoms of asthma in a rodent model. *Pharm Res* 31:3095 105.
- Patil Gadhe A, Kyadarkunte A, Patole M, Pokharkar V. (2014). Montelukast loaded nanostructured lipid carriers: Part II Pulmonary drug delivery and invitro in vivo aerosol performance. *Eur J Pharm Biopharm* 88:169 77.
- Patil Gadhe A, Pokharkar V. (2014). Montelukast loaded nanostructured lipid carriers: part I oral bioavailability improvement. *Eur J Pharm Biopharm* 88:160 8.
- Pawankar R. (2014). Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J* 7:12.
- Phipatanakul W, Nowak Wegrzyn A, Eggleston PA, et al. (2002). The efficacy of montelukast in the treatment of cat allergen induced asthma in children. *J Allergy Clin Immunol* 109:794 9.
- Pizzichini E, Leff JA, Reiss TF, et al. (1999). Montelukast reduces airway eosinophilic inflammation in asthma: a randomized, controlled trial. *Eur Respir J* 14:12 8.
- Priyanka K, Sathali AAH. (2012). Preparation and evaluation of montelukast sodium loaded solid lipid nanoparticles. *J Young Pharm* 4:129 37.
- Ranjan OP, Nayak UY, Reddy MS, et al. (2014). Osmotically controlled pulsatile release capsule of montelukast sodium for chronotherapy: statistical optimization, in vitro and in vivo evaluation. *Drug Deliv* 21: 509 18.
- Rao NGR, Suryakar VB. (2010). Formulation and evaluation of montelukast sodium mucoadhesive buccal patches for chronic asthma attacks. *Int J Pharm Bio Sci* 1:1 14.
- Rao NGR, Suryakar VB. (2011). Design and development of mucoadhesive drug delivery system of montelukast sodium. *Int J Res Ayurveda Pharm* 2:491 7.
- Rao NGR, Suryakar VB, Thube K. (2010). Development of mucoadhesive films for buccal administration of montelukast. *Int J Pharm Technol* 2:1 15.
- Rashmitha N, Raj TJS, Srinivas C, et al. (2010). A validated RP HPLC method for the determination of impurities in montelukast sodium. *E J Chem* 7:555 63.
- Schoch GA, Yano JK, Sansen S, et al. (2008). Determinants of Cytochrome P450 2C8 Substrate binding: structures of complexes with montelukast, troglitazone, felodipine, and 9 cis retinoic acid. *J Biol Chem* 283:17227 37.
- Shravani B, Rao NGR. (2014). Formulation and evaluation of fast dissolving tablets of montelukast sodium using co processed super disintegrants. *Int J Drug Dev Res* 6:125 34.
- Siddiqui MN, Garg G, Sharma PK. (2011). A short review on a novel approach in oral fast dissolving drug delivery system and their patents. *Adv Biol Res* 5:291 303.
- Simons FER, Villa JR, Lee BW, et al. (2001). Montelukast added to budesonide in children with persistent asthma: a randomized, double blind, crossover study. *J Pediatr* 138:694 18.
- Soni R, Sagar GV, Sharma P. (2012a). In vitro permeability and pharmacodynamic assessment of stable mucoadhesive bilayered buccal patches of montelukast sodium. *Int J Res Pharm Biomed Sci* 3: 1387 96.
- Soni R, Sagar GV, Sharma P. (2012b). Formulation, development and evaluation of mucoadhesive bilayered buccal patches of montelukast sodium. *Int J Pharm Pharm Sci* 2:484 97.
- Sri KV, Raj GB, Ravishanker D, Kumar CA. (2012). Preparation and evaluation of montelukast oral dispersible tablets by direct compression method. *Int Res J Pharm* 3:315 18.
- Storms W. (2007). Update on montelukast and its role in the treatment of asthma, allergic rhinitis and exercise induced bronchoconstriction. *Expert Opin Pharmacother* 8:2173 87.
- Storms W, Michele TM, Knorr B, et al. (2001). Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged > 6 years. *Clin Exp Allergy* 31:77 87.
- Thun J, Milius W, Wedel B, et al. (2009). The crystal structure of the API Montelukast. *Cryst Eng Comm* 11:1306 8.
- US Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Nomenclature Standards Committee, 1998.
- US Food and Drug Administration. 2016. Code of Federal Regulations: 21 C.F.R. §§ 170.30(b) and 170.3(h). [Revised as of April 1, 2015].
- van Adelsberg J, Moy J, Wei LX, et al. (2005). Safety, tolerability, and exploratory efficacy of montelukast in 6 to 24 month old patients with asthma. *Curr Med Res Opin* 21:971 9.
- Villiers A. (1891). Sur la fermentation de la fécule par l'action du ferment butyrique. *Compt Rend Acad Sci* 112:536 8.
- Weber S, Zimmer A, Pardeike J. (2014). Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for pulmonary application: a review of the state of the art. *Eur J Pharm Biopharm* 86:7 22.

- Wenzel SE. (2003). The role of leukotrienes in asthma. *Prostaglandins Leukot Essent Fatty Acids* 69:145–55.
- Xiao L, Wang B, Yang G, Gauthier M. (2012). Poly(Lactic Acid) based biomaterials: synthesis, modification and applications. In: Ghista DN, ed., *Biomedical science, engineering and technology*. InTech (online ed.), Chapter 11, 247–82. Available at: <http://www.intechopen.com/books/biomedical-science-engineering-and-technology/poly-lactic-acid-based-biomaterials-synthesis-modification-and-applications>.
- Young RN. (2001). The discovery of montelukast (Singulair): a leukotriene receptor antagonist for the treatment of asthma. Séminaires & Conférences Chimie École Doctorale 459, Université de Montpellier II, 2009 Sep 29, Montpellier, France.
- zur Muhlen A, Schwaz C, Mehnert W. (1998). Solid lipid nanoparticles (SLN) for controlled drug delivery drug release and release mechanism. *Eur J Pharm Biopharm* 45:149–55.